FINAL PUBLISHABLE SUMMARY REPORT

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1. Executive summary

Diabetes mellitus is a chronic disease characterised by the inability of the organism to autonomously regulate the blood glucose level due to insulin deficiency (Type 1) combined with insulin resistance (Type 2), thus leading to serious health damages and very high personal and enormous social costs. It affects millions of patients in Europe and the rest of the world, a number expected to increase significantly in the coming years.

From onset of Type 1 and during late progression of Type 2 diabetes, treatment is based on insulin. Tight control of blood glucose concentration is needed to prevent short and long term health complications. In spite of continuous improvements in insulin preparations, delivery devices and monitoring of blood glucose, insulin therapy remains one of the most difficult therapies to manage. This is because treatment outcome strongly depends on the patient's skill in making daily decisions about insulin delivery. Availability of a device empowering the patients to make the most adequate decisions can potentially contribute to better treatment outcomes, reduced complications and health costs.

Against this background, the DIAdvisor[1] project has developed a personalised on-the-spot handheld blood glucose predicting and treatment advisory system, utilising minimally invasive sensors registering physical information, mathematical models for prediction of short-term blood glucose levels and calculating treatment advices.

Testing of the DIAdvisor prototype in a short term feasibility trial has demonstrated that blood glucose predictions, more than 40 minutes ahead and advises of high quality, are achievable. Furthermore, a randomized control clinical trial including 57patients has demonstrated that time spent in debilitating hypoglycaemia can be reduced by about 40%, time spent in normal blood glucose range can be increased by about 8% and time spent in hyperglycaemia inducing long term complications can be reduced by about 9%.

Extending the treatment improvements found in the latter DIAdvisor clinical trial to longer periods, the effect of providing BG prediction and advice can be translated to overall better blood glucose control leading to better treatment outcomes, potential reduced complications and eventual higher quality of life and lower health costs.

[1] The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7) under grant agreement n° 216592.

2. Abbreviations

BG	Blood Glucose
bpm	beats per minute
CGM	Continuous Glucose Measurement
CG-EGA	Continuous Glucose-Error Grid Analysis
CRC	Clinical Research Centre
DAFNE	Dose Adjustment For Normal Eating
DAQ	Data Acquisition Trial
DCCT	Diabetes Control and Complications Trial
DIAdvisor	Personal Glucose Predictive **Dia**betes **Advisor**
DIAdvisor1	First DIAdvisor™ in-vivo trial
DIAdvisor2	Second DIAdvisor™ in-vivo trial
DM	Diabetes mellitus
eAG	estimated Average Glucose
EU	European Union
FP7	7th Framework Program
FTP	File Transfer Protocol
HbA1c	Hemoglobin A1c
HBGI	High Blood Glucose Index
HCP	Health Care Provider, health centre, medical advisor, nurse, doctor
IPR	Intellectual Property Rights
LBGI	Low Blood Glucose Index
MDD	Medical Device Directive
MOMM	Modified Oral Minimal Model
MPC	Model Predictive Control
OMM	Oral Minimal Model
SD	Standard Deviation
SMBG	Self Monitoring of Blood Glucose
Type 1 diabetes	Insulin depended diabetes, juvenile diabetes
Type 2 diabetes	Adult-onset diabetes, obesity related diabetes
UMPC	Ultra Mobile PC
WP	Work Package
YSI	Yellow Spring Instrument glucose analyser

3. Summary Description of Project Context, Objectives and Outcome

3.1 Diabetes mellitus – a global health problem

Diabetes mellitus (DM) is a chronic disease characterised by the inability of the organism to regulate autonomously the blood glucose level due to insulin deficiency or resistance, thus leading to serious health damages and very high personal and enormous social costs. It affects currently 366 million patients worldwide and is expected to affect around 552 millions by 2030[2]. A study[3] performed in eight European countries reported that in 1999, around €29 billion were spent in these countries for direct medical costs related to diabetes, i.e. a yearly estimated cost of €2.834 per patient. Of note, 55% of these expenses were due to hospitalisations related to diabetes. Moreover, the CODEIRE study[4] performed in Ireland reported that a diabetic patient affected by microvascular or macrovascular complications was responsible for a cost 1.8 or 2.9 times that of a non-complicated patient, respectively. Average cost related to a patient affected by both types of complications reached 3.8 times that of a non-complicated patient.

From the beginning of Type 1 diabetes or during disease progression of Type 2 diabetes, treatment happens to be based essentially on insulin delivery. Large intervention trials performed in EU[5] and US[6] showed how tight control avoiding hyperglycaemia, could prevent long term complications, but also reported the associated risk of induced hypoglycaemia that underscores the crucial need of exact and timely insulin dosage.

Insulin therapy is vital for patients affected by Type 1 diabetes, essential for blood glucose control and prevention of complications in many Type 2 diabetic patients and extremely, valuable for non-diabetic patients in critical situations that impair physiological glucose homeostasis like intensive care. However, in spite of continuous improvements in insulin preparations (insulin analogues), insulin delivery devices (user-friendly insulin pens, wearable pumps) and monitoring of blood glucose (capillary blood glucose measurements, glucose sensors for continuous monitoring), insulin therapy remains one of the most difficult therapies to manage. While treatment targets become narrower to mimic normal glucose variations, fine-tuning of insulin delivery requires an increased availability of data on blood glucose and multiple factors that influence insulin effectiveness. Moreover, slight deviations of blood glucose out of aimed target range (normal[7] blood glucose level) have a quick and dangerous impact on patient status (hypoglycaemia), and long term impact on health outcome[8] (hyperglycaemia).

Because sustained hyperglycaemia is associated with severe long-term outcomes (retinopathy, nephropathy, neuropathy, cardiovascular complications), intensive insulin therapy aiming at near-

[2] IDF report 2011

[3] Jönsson B on behalf of CODE-2 Advisory Board. Revealing the cost of Type 2 diabetes in Europe. Diabetologia 2002, 45: S5-S12.

[4] Nolan JJ, O'Halloran D, Mc Kenna TJ, Firth R, Redmond S. The cost of treating type 2 diabetes (CODEIRE). Ir Med J 2006, 100: 307-10

[5] UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with Type 2 diabetes (UKPDS 33). The Lancet 1998, 352 : 837-53.

[6] The Diabetes Control and Complications Trial Research Group.The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329, 977-86.

[7] Corresponding to 3.5-and 7 mmol/l corresponding to a HbA1c level below 6.3%. Note that not only the mean values, but also the deviations are associated to glucose control .

[8] Retinopathy (most frequent cause of new cases of blindness in adults), nephropathy (most frequent cause of end stage renal disease), neuropathy (most frequent cause), cardiovascular complications (most frequent cause of non-traumatic amputations, pre-diabates present in two thirds of people who had a heart attack)

normoglycaemia has been strongly promoted during the last decades, following the report of the results of Diabetes Control and Complications Trial[9]. This strategy is based on reinforcement of treatment goals aiming at tight blood glucose targets, use of multiple daily insulin injections or insulin pumps, multiple daily SMBG, assistance to the patient from a health care team via frequent visits and 'phone calls. However, more frequent occurrence of severe hypoglycaemic events, tendency to gain weight, lack of improved quality of life associated with DCCT-like intensive insulin therapy as well as insufficient availability of health care providers to fulfil expected assistance of patients, preclude the feasibility of this strategy in common practise. Post-DCCT follow-up of patients, reported in EDIC, clearly showed the failure to maintain tight HbA1c control in everyday life after the clinical trial[10].

Although therapeutic devices improved during the last decades, this therapy still strongly depends on the patients' daily decisions about insulin delivery adaptations. Many factors have to be considered in this decision process: current blood glucose level, aimed blood glucose target, insulin sensitivity according to health status, foreseen activities and individual experience of insulin effects on blood glucose level. The patient's personal skill in taking into account these various influences is a result of therapeutic education, knowledge of therapeutic goals, coaching of health care providers and cumulated experience about insulin use. Meanwhile, failure in management of insulin therapy has significant impacts on short-, medium- and long-term prospects, such as debilitating hypoglycaemia, impaired well-being and long term complications related to chronic hyperglycaemia, respectively. Long term, each reduction of HbA1c by 15% would lead to a 10% reduction in diabetic complications[11].

Patient empowerment in therapeutic management is nowadays agreed to be a solution to compensate for the limited availability of health care providers. This transfer of competence implies at first a thorough patient education on how to manage insulin therapy according to SMBG results and food intakes. DAFNE experience in United Kingdom documented some benefits of this approach: improved HbA1c levels and quality of life, no increase of severe hypoglycaemia and lack of weight gain[12]. However, the reached HbA1c targets remained too far from normoglycaemia and education effects hardly persisted more than 6 months.

From these observations, patient empowerment may represent an effective option only if associated with available assistance to make the right decisions about treatment. Experiences have been reported using 'Call Centres' that patients may contact for getting some help to manage their therapy. Although some benefits have been reported about diabetes acceptance, glycaemic control did not improve significantly or remained far from the optimal goal in most studies[13] [14] [15].
From the current needs and the overall lack of an available device to empower diabetic patients in adapting accurately their insulin delivery, the elaboration of a safe and effective blood glucose predictor and advisor that could inform at any time the patient about the most adequate choice of insulin delivery to reach glucose targets would represent a valuable initiative.

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[9] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993 ; 329 : 977-86.

[10] Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of Type 1 diabetes mellitus. JAMA 2002; 287: 2563-9.

[11] Diabetes Control and Complications Trial (1983-1993) http://diabetes.niddk.nih.gov/dm/pubs/control/

[12] DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with Type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial.BMJ 2002; 325: 746.

[13] Howells L, Wilson AC, Skinner TC, Newton R, Morris AD, Greene SA. A randomized control trial of the effect of negotiated telephone support on glycaemic control in young people with Type 1 diabetes. Diabet Med 2002;19: 643-8.

[14] Farmer AJ, Gibson OJ, Dudley C, Bryden K, Hayton PM, Tarassenko L, Neil A. A randomized controlled trial of the effect of real-time telemedicine support on glycemic control in young adults with Type 1 diabetes (ISRCTN 46889446). Diabetes Care 2005; 28: 2697-702.

[15] Montori VM, Helgemoe PK, Guyatt GH, Dean DS, Leung TW, Smith SA, Kudva YC. Telecare for patients with Type 1 diabetes and inadequate glycemic control: a randomized controlled trial and meta-analysis. Diabetes Care 2004; 27:1088-94.

3.2 DIAdvisor Concept

Against this background, the DIAdvisor project aims at developing a personalised blood glucose predicting and advisory system, which can be used on the spot to assist a patient with diabetes, and help them to manage their disease, effectively minimise time spent outside the normal glycaemic range, optimising safety and giving an improved quality of life.

Therefore, the DIAdvisor system must be a handheld device like a PDA (Personal Digital Assistant) or a mobile phone, which the patient has along anyway during the day. The system will need user input (e.g. meal and insulin dosing) and inputs from sensors to work. To ensure that the system works in a real setting, effort must be put into the development of small wireless system with an easy and intuitive user interface.

The main progress expected from this project is to satisfy this need developing a system which:

- sets no additional burden on the patient, hopefully even reduces it
- merges easily available information
- works predictively, considering not only instantaneous effects, but also their consequences in the near future, thus
- yielding a much tighter control thus improving life quality and health costs
- interfaces to the health service, allowing an easier monitoring of the illness

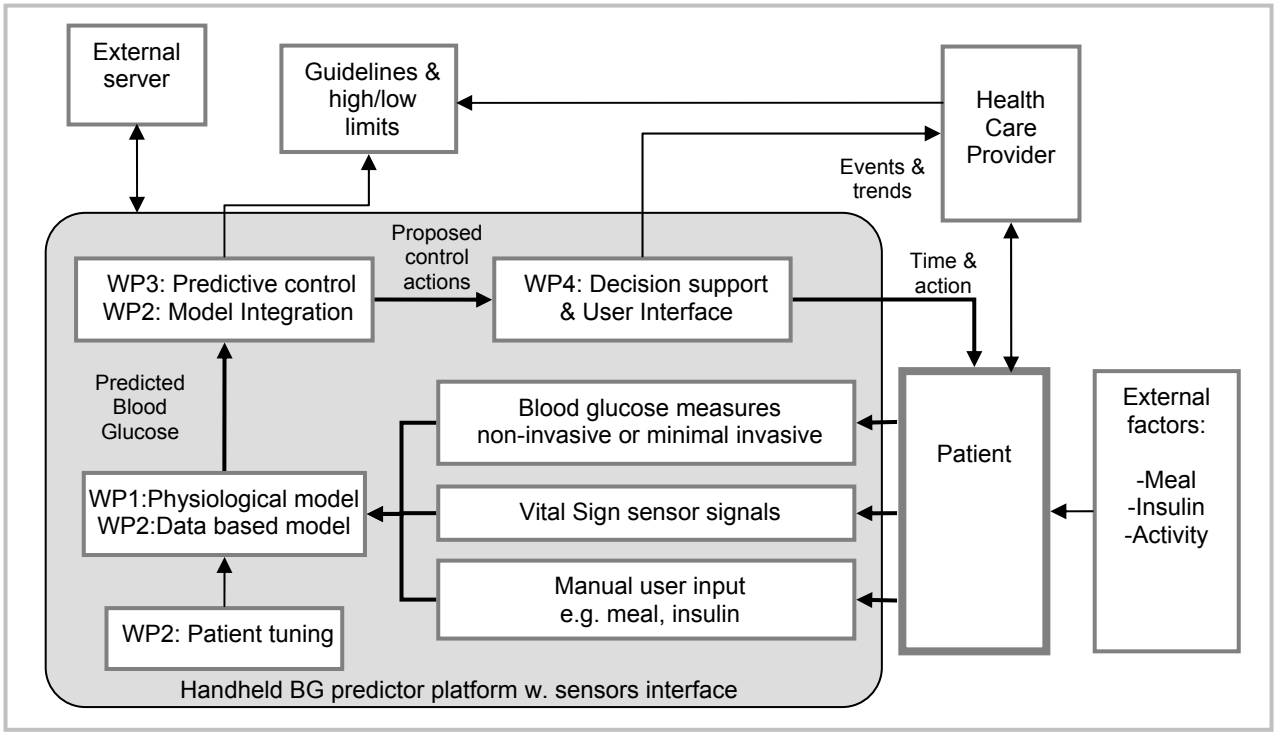

Figure 1: The DIAdvisor concept overview

The flow through the DIAdvisor system as shown in 0 can be divided into three steps:

1. Input from vital sign sensors and blood glucose measurements acquired from the patient
2. A prediction engine consisting of a mixed model combined with a predictive control algorithm, predicting future blood glucose development and computing suitable corrective actions.

3. The predicted BG curve and corrective action is interpreted by a decision support module, which based on expert knowledge and the predicted BG curve, come up with suggestions to the user when the patient is moving away from a preset target range and an action is needed to get the BG value on track again.

The BG predictor engine will need an initial tuning phase on each individual patient before it can be used in an everyday situation.

Wireless communication of patient parameters to the HCP provides important information about trends and events to increase the efficiency of counselling and makes it possible to monitor the patient and interfere if needed.

The price to pay for these improvements is essentially the complexity of the algorithms, which cannot any longer be simple rules of thumbs but need to be comprehensive algorithms representing the patients metabolism and these must be tailored to the individual patient and the actual conditions.

Although seemingly simple in concept, the problem of glucose prediction in an active individual has to date proved intractable. To overcome this, advanced approaches based on physiological models will be complemented by up-to-date methods arising from identification theory, control theory, advanced medical device technology, risk management theory, sensor science, comprehensive user understanding and other science fields.

3.3 Project structure

In Figure 1 the task distribution and relation between Work Packages is indicated. This is in more details described in Table 1. The outcome of each Work Packages will be discussed in details the following sections.

WP	Task	WP Leader	Primary partners
1	Physiological models for prediction, control and testing	UNIPD-DEI	NNAS
2	Data based model for prediction Model Integration	ULUND	JKU, RICAM
3	Predictive control models	JKU	ULUND
4	Hardware and software for clinical trial systems including sensors, decision support models and user Interface	TOUMAZ	ONDALYS, INT, NNAS
5	Clinical data acquisition for model development and clinical testing of system	CHU	IKEM, UNIPD-DMCS

Table 1: Task distribution between Work Packages

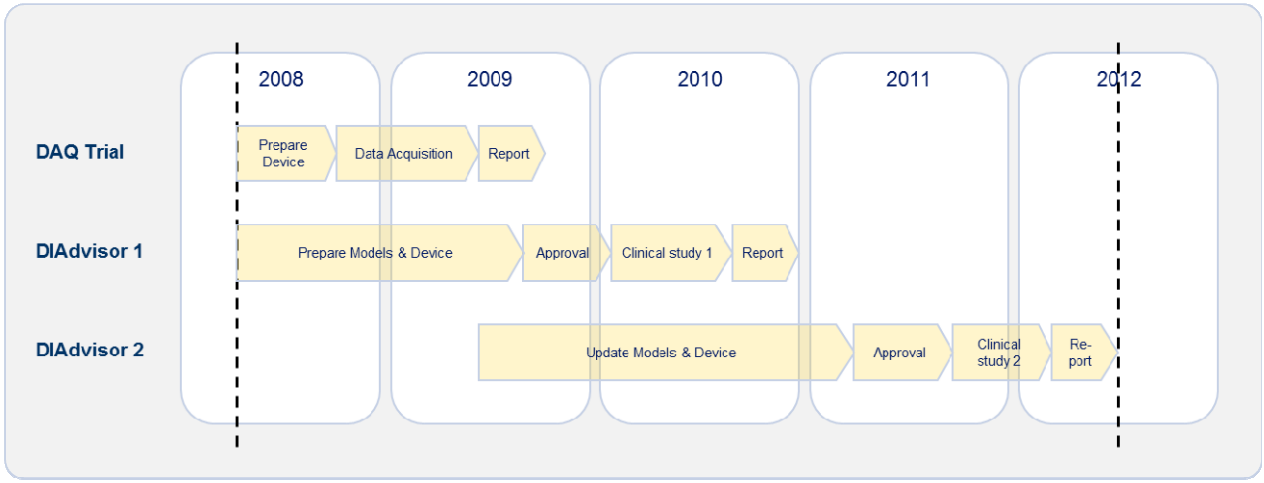

Figure 2: Project phases

The flow through the development phases of the project is shown in Figure 2. As can be seen the project was divided in three major but overlapping phases:

1. Data Acquisition Trial (DAQ): Collection of rich interrelated physiological data to be used for development of the DIAdvisor prediction and control algorithms
2. DIAdvisor1: The first DIAdvisor prototype tested in clinic to verify concept, functionality and performance
3. DIAdvisor2: Taking experience and learning's from DIAdvisor1, implementing it in the system and taking it into account in the DIAdvisor2 trial aiming at validating the effect of prediction and advice on treatment outcome.

3.4 Objectives and Outcomes

The overall project objectives and outcomes fall in three categories and can be summarised as follows:

Objective	Outcome
1. Technological objectives - Development of a software model for a Blood Glucose Prediction and Advisory engine based on: Physiological modelling (WP1), modelling based on clinical data (WP2) and predictive control (WP3). - Realisation of a DIAdvisor device platform (WP4) including vital sign and blood glucose sensors. The DIAdvisor should be based on an existing PDA or cell phone and existing and new sensors o First iteration where models and advisory algorithms will be generated using available clinical data to a stage where it can be approved for clinical	This has been successfully achieved by WP1, WP2 and WP3. A detailed description can be found in this reports section 4.1, 4.2 and 4.3 respectively

Objective	Outcome
tests according to MDD. o Second iteration where the system will be improved based on learning's from first iteration	
2. Social objectives - Providing the DIAdvisor system as a medical device that minimises diabetes-related burdens to the diabetic patient (individual benefit on quality of life) and to healthcare systems (societal benefit) by increased patient empowerment in health management. Specific objectives that will reduce diabetes-related complications and associated costs: o estimated Average Glucose (eAG)[16] decreased by at least 10% - randomised controlled clinical trials o Occurrence of hypoglycaemic events reduced by 20% - randomised controlled clinical trials o Average time outside normal glucose range reduced by 20% - randomised controlled clinical trials	Through clinical testing, the DIAdvisor systems capability of data capture, glucose prediction on short-term horizon and patient advising on treatment adjustments has been validated. Through a short randomized controlled trial, significant improvements in glucose control has been achieved o Average time in hypoglycaemia reduced by about 40% o Average time in hyperglycaemia reduced by about 9% o estimated Average Glucose, however, did not show improvements as the involved patient populations turned out already to be in normal range These outcomes are further described in section 4.5
3. Exploitation and use objectives - Preparing requirement specifications for the DIAdvisor system for future product development (WP4). - Preparing an exploitation / IPR strategy for the industrial partners. - Prepare project presentations (website, brochures) and scientific papers. - Perform training courses and investigators brochures for users (patients and clinical personnel).	These objective has been successfully met and includes more than 80 scientific publications and 3 patent applications More details can be found in section 4.

Table 2: Objectives and Outcomes

[16] As HbA1c is difficult to determine in short clinical trials, "estimated Average Glucose" (eAG) that is well correlated with HbA1c is usable as surrogate ("Translating the A1C Assay Into Estimated Average Glucose Values" by David M. Nathan, Diabetes Care 31:1473–1478, 2008)

4. Scientific and Technical Foregrounds

4.1 Work Package 1 – Physiological Modelling

Prof. Claudio Cobelli, University of Padova, including NNAS, JKU, ULUND, UNIPD-DEI, UNIPD-DMCS, CHU, RAMBOLL

4.1.1 Introduction

The purpose of Work Package 1 (WP1) was:

1. To develop physiological models of the glucose-insulin system which can be incorporated into glucose predictors and controllers, developed in other work packages (WP2 and WP3).
2. To develop a real life simulator of the glucose-insulin system to provide the test bed for in silico assessment of the performance of predictors and advisory systems provided by WP2 and WP3.

In this section we summarise the main results achieved by WP1 into the DIAdvisor project and show that, we reached the two main goals listed above.

4.1.2 Development of physiological models of the glucose-insulin system to be incorporated into glucose predictors and controllers

For what concern this first goal, we discussed with WP2 and WP3 to understand their requirements.

Models of the glucose-insulin system to be incorporated into glucose predictors
We agreed with WP2 to provide two Matlab routines, that we called Glucose Rate of Appearance and Plasma Insulin Generator.

Glucose Rate of Appearance Generator
The Glucose Rate of Appearance Generator transforms the knowledge on the administered glucose dose into the corresponding meal glucose rate of appearance using a physiological model of glucose transit through the gastro-intestinal tract [1].

In particular, at each instant t_{k-1}, given the initial state vector and the amount of ingested glucose, the function generates prediction of meal glucose rate of appearance in the interval $[t_k; t_k+T]$, where T is the user defined prediction horizon.

Plasma Insulin Generator
The Plasma Insulin Generator transforms the knowledge on the administered insulin boluses and basal rate into the corresponding plasma insulin concentration using a physiological model of subcutaneous insulin kinetics [2]. The routine can simulate insulin profile both in case of multi-injective (both fast acting and slow acting insulin analogues) and pump therapy (only fast acting insulin analogues). In fact, at each step, two simulations are performed, the first generates the profile of fast acting insulin, and the second provides the slow acting insulin concentration. These two simulated profiles are then summed up to provide total plasma insulin concentration.

In particular, at each instant t_{k-1}, given the initial state vector and the amount of injected insulin, the function generates prediction of plasma insulin concentration in the interval $[t_k; t_k+T]$ where T is the user defined prediction horizon.

Other models of subcutaneous insulin kinetics, in addition to that described in [2] and implemented in the routine, have also been tested to assess if model individualisation was possible based on anthropometric characteristics or patient specific parameters (i.e. insulin to carb ratio, correction factor, basal insulin infusion). Our analysis showed no clear pattern in order to obtain a more individualised model. Furthermore the investigations showed that the model currently implemented in the "Plasma Insulin Generator" is the best model for the use within DIAdvisor, although there is still room for improvement in the context of glucose prediction.

Dissemination of the results
Results have been presented at the 10th Diabetes Technology Meeting in November 2010 [3].

Models of the glucose-insulin system to be incorporated into glucose controllers
Upon request from WP3 partners, a low order (6 states) model of the glucose-insulin system has been developed. It can be embedded in the MPC block which suggests the optimal insulin infusion rate to the insulin pump.

A simplified version of the simulation model of glucose-insulin system [4] was implemented in Matlab and tested on DAQ Trial data. The glucose kinetics is described with a single compartment that is fed by the rate of appearance. The glucose uptake is mediated by the insulin action X(t) (a delayed version of plasma insulin profile). The uptake is also nonlinearly dependent on the amount of glucose in plasma (Michaelis-Menten). The gastro-intestinal tract is described with a single compartment and the transfer rate of glucose from the intestine to the circulation is nonlinearly dependent on the amount of glucose in the gastro-intestinal tract. A two compartment model is used to describe insulin kinetics and subcutaneous absorption and a single compartment model describes plasma-interstitium glucose dynamics.

Model Assessment
The model was identified on DAQ Trial data. The 3 in-hospital days were considered, and each meal was identified separately. Despite the simplicity of the model, the predictions of glucose, insulin and CGM were acceptable for the purpose for which the model was built.

With the parameters obtained from the identified subjects, a simulation was performed to test if the model correctly spans the glucose range observed in the DAQ trial. Mean measured glucose and insulin profiles and the relative ±SD envelope were compared with the correspondent simulated profiles, confirming that the model correctly describes the overall glucose and insulin dynamics.

Dissemination of the results
Results have been presented at the 3rd International Conference on Advanced Technologies & Treatments for Diabetes in February 2010 [5].

4.1.3 Development of a real life simulator of the glucose-insulin system to provide the test bed for in silico assessment of the performance of predictors and advisory systems

The planned refinement/validation of the in silico model of glucose-insulin system [4] against tracer data generated into DIAdvisor project was not possible, as [6,6-2H2]-glucose were not available from the DAQ trial, due to technical problems in measuring molar ratios in plasma. Nevertheless,

as discussed below, we were able to study inter- and intra-subject variability of key metabolic parameters to describe sensor noise and calibration error and include this knowledge in the simulator. The reliability of the simulator was then assessed by comparing the simulated with the measured glucose profiles. Thus, we believe that WP1 did important scientific progress within DIAdvisor project also for what concerns the real life simulator and substantially achieved the goals of the WP listed above.

Inter- and Intra-subject Variability of Key Metabolic Parameters
The aim was to obtain information on intra-subject variability of insulin sensitivity and gastro-intestinal parameters, in absence of glucose-tracer data. To this purpose, the Oral Glucose Minimal Model (OMM) [6] has been modified by replacing the piece-wise linear description of the glucose Rate of Appearance with a more physiological model of the gastrointestinal glucose absorption (Modified Oral Minimal Model, MOMM). The model was identified on DAQ trial data provided by WP5. Each subject was studied for 3 days in hospital. Data from each meal were identified separately, thus for each subject 9 model parameter sets were available.

When considering the meals separately (breakfast, lunch and dinner), some circadian variations of the identified model parameters, in particular insulin sensitivity, were observed. Similarly, for gastro-intestinal model parameters we found that gastric emptying and intestinal absorption at lunch and dinner are lower than at breakfast. These results have allowed to introduce some circadian variation in the simulator (see section 'From a 6-hour to a 3-day Simulator' below).

Dissemination of the results
Results have been presented at the World Congress 2009 Medical Physics and Biomedical Engineering [7].

Sensor Noise and Calibration Error
The calibration error in the CGM signals of Freestyle Navigator device was analysed and modelled as an offset and a stretch in the in silico model. Calibration error profiles were added to the traces in order to challenge the predictors and the controller in suboptimal conditions.

In addition, the usefulness of sensor tracer recalibration was investigated since the analysis of the DAQ Trial database showed that Navigator CGM data are often not sufficiently accurate. This could affect the performance of the DIAdvisor device. "External" on-line recalibration procedures of CGM signals could be used to improve the outcome of the CGM sensor. In order to test the potential usefulness of such a recalibration procedure within DIAdvisor, a subset of CGM Navigator traces were processed by a retrospective literature recalibration method and improved accuracy was demonstrated by CG-EGA. The recalibrated CGM Navigator signals were provided to partners.

From a 6-hour to a 3-day Simulator
A 3-day simulator was developed starting from the 6-hour simulator model described in [4]. To do that, we incorporated the knowledge gained from the identification of MOMM and sensor error analysis described above. This can be summarised as follows:

- Circadian (systematic) variation of the key parameters of the model
- Random variations of all parameters
- Plausible addition of sensor error

With this modification, the simulated plasma glucose and CGM profiles reasonably reflect the traces variability observed in the DAQ trial.

Physical Activity
To develop a model of physical activity on glucose metabolism, we used the data of DIAdvisor protocol 1D, provided by WP5. In that protocol, each patient received a standardised meal with insulin bolus administered according to subject own insulin to carbs ratio. Three hours and 30 minutes later subject underwent to an exercise session which ended 30 minutes later. Plasma glucose and insulin concentrations were measured in each sample with standard techniques. Heart rate was measured using Toumaz Life Pebble sensor based on two ECG electrodes.

The model selected to describe the effect of physical activity on glucose dynamics assumes that, in presence of physical activity, the heart rate modulates, with some delay, insulin action.
Such knowledge has been incorporated into the type 1 diabetes simulator.

With this updated simulator, virtual trials including physical activity can be performed. For instance, the two following scenarios have been simulated: the 100 in silico subjects received a meal containing 70 g of CHO at time 0 and injected the appropriate amount of insulin, according to the subject-specific carbs to insulin ratio; 3 hours after the meal the virtual subjects had a 30 minutes exercise session, mild (assuming to increase heart rate to 100 bpm) in the first and moderate (assuming to increase heart rate to 140 bpm) in the second scenario. However, different HR response to exercise can be easily implemented. As expected, moderate exercise produces a larger drop in glucose concentration than the mild exercise.

Average plasma glucose profiles and ±SD bands of the 100 in silico patients which underwent the above described scenarios are comparable to those observed during DIAdvisor1D trail.

Dissemination of the results
Results have been obtained only recently and for this reason they have not been documented in conference/journals papers yet. This will be done in the next future.

4.1.4 Conclusions

The main objectives of WP1 have been achieved. In particular, we developed physiological models of the glucose-insulin system which can be incorporated into glucose predictors and controllers and a real life simulator of the glucose-insulin system to provide the test bed for in silico assessment of the performance of predictors and advisory systems.

The results obtained by WP1 within the DIAdvisor are scientifically relevant and part of them have been presented at international conferences (Diabetes Technology Meeting and Advanced Technology & Treatments for Diabetes), where they earned the interest of the scientific community.

4.1.5 References

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[7] Guerra S., Dalla Man C., Sparacino G., Renard E., and Cobelli C., The oral glucose minimal model in Type 1 diabetes: an ingredient of DIAdvisor, World Congress 2009, Medical Physics and Biomedical Engineering, 7-12 September 2009.

4.2 Work Package 2 – Data Based Modelling and Integration

Prof. Rolf Johansson – University of Lund, including NNAS, JKU, ULUND, UNIPD-DEI, RICAM, RAMBOLL

4.2.1 Introduction

The objectives of WP2 were to determine patient-specific data-based models of diabetic subjects, for classification and development of short-term predictors of blood glucose concentration. The identification methods should be applicable to data records of blood glucose concentration from various measurements devices, thus providing empirical models for calibration of short-term blood glucose predictors. DIAdvisor results on physiological modelling of insulin flux and glucose rate of appearance in the gut were integrated.

The purpose of the prediction is to systematically combine known diabetic physiology and current measurement to provide a helpful prediction of the course of change in blood glucose over a time horizon up to four hours. Natural basic limitations are that the predictors must be patient-specific and that the prediction accuracy will decline over longer prediction horizons.

In Figure 3, an example of what a blood glucose prediction may look like on the users personal device.

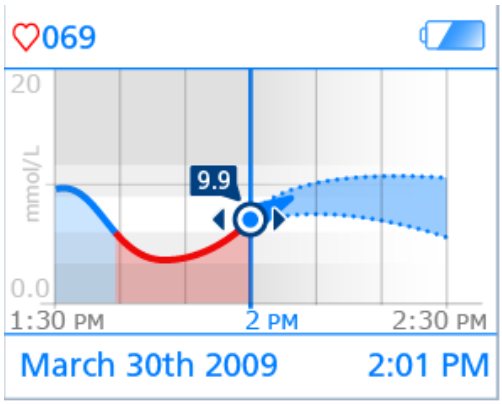

Figure 3: Screen dump from the DIAdvisor device: Example of prediction including confidence interval.

The main challenge of WP2 was to provide algorithms for short-term glucose predictions to the DIAdvisor platform. To this end, several linear and nonlinear models have been investigated and developed, incorporating physiologically based models as well as data-driven black-box models. For the final clinical tested DIAdvisor prototype three different prediction models were included:

- A regularised kernel-based approach (RKB)
- A linear state space predictor (SS)
- A nonlinear ARX-predictor (NARX)

Based on the various prediction models and complexity, a variety of subject-specific predictors were developed and validated. Once predictors are tuned to patient-specific data, they are invoked in the DIAdvisor system, providing new real-time predictions based on the identified model and new measurements.

Not surprisingly, the predictor performance of each predictor may change over time and it may be difficult to single one predictor outperforming the other predictors. Consequently, multiple different predictors run in parallel, utilising different techniques, and relying on different types of input data to predictions for the range of 10 to 120 minutes ahead. The state-space (SS) predictor [1] was developed based on a methodology derived in [2], the NARX predictor outlined in [3] and the RKB predictor in [4]. All three models rely on a stream of glucose data from the CGM-sensor, and the former two models also take into account insulin and meal data, utilising physiologically-derived models provided by WP1 of insulin pharmacokinetics and glucose rate of absorption from the gut following a meal.

Data analysis and sensor evaluation with attention to variables other than glucose flux and insulin absorption profile relevant in the description of the system were also considered. Model accuracy and quality were characterised with statistical and clinically-oriented prediction error analysis with special attention to the quality and accuracy of short-term prediction. An example of prediction quality obtained for various prediction horizons are given in the diagram below. The very good predictive properties of the prediction horizons of 30-60 min deteriorate somewhat for the longer prediction horizons of 60-120 min while still proving good and helpful predictions.

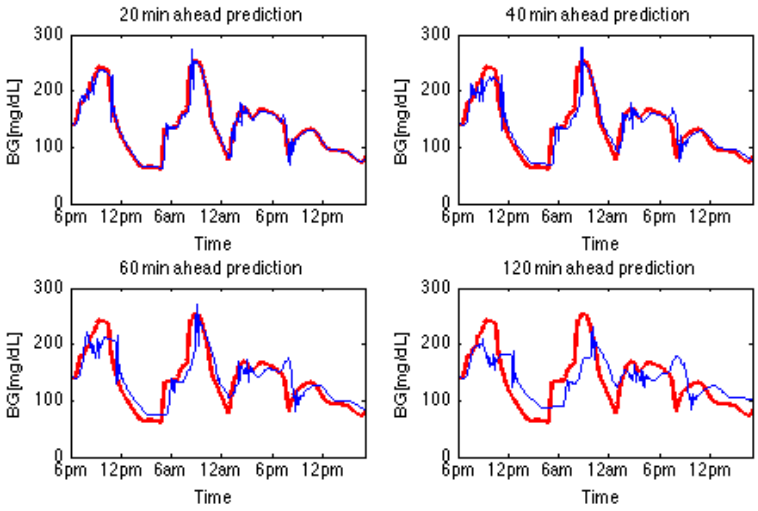

Figure 4: Patient CHU0102. Evaluation on validation data. 3-rd order ARMAX-based predictor (thin blue) and measured plasma glucose (thick red) [mg/dl] vs. time [min]

In order to take advantage of the multiple predictors developed in the project, model integration was addressed. The task was accomplished by a separate integration software module implemented in the DIAdvisor concept, which based on Bayesian techniques merges the different predictions by linear weighting into a single unique outcome. Each predictor weight is determined using an optimisation approach taking into account the predictive quality of every individual predictor for the most recent data. The final prediction (hereafter simply the DIAdvisor prediction) is presented with upper and lower confidence limits, see Figure 6.

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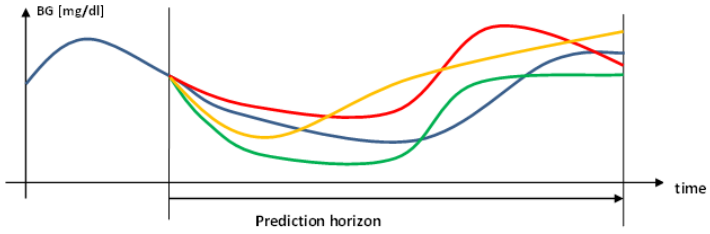

Figure 5: Example of predictions. Blue curve: Patient glucose excursion data. Green/Red/Yellow curves: Model predictions

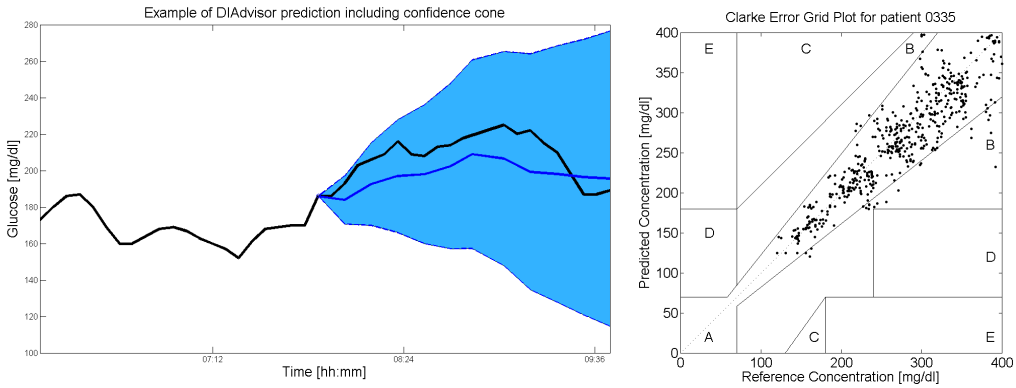

Figure 6: Left: Example of DIAdvisor prediction (blue curve) including confidence bound (shaded area) vs. CGM (black curve). Patient 46 from Montpellier. Right: DIAdvisor Prediction evaluated with Clarke Error Grid Analysis. Patient 35 from IKEM, Prague.

4.2.2 Online Evaluation on DIAdvisor1 and 2 data

The integrator concept was implemented in the DIAdvisor platform and has been validated in the clinical trials DIAdvisor1 and DIAdvisor2. The performance of the DIAdvisor prediction has been evaluated by the Clarke-EGA (Clarke Error Grid Analysis) criteria, using the frequent YSI reference measurements as the prediction target. In the DIAdvisor1 trial the primary endpoint (zone A+B>80 %, zone E: <5 % in the 70-180 mg/dl range) has been confirmed. This has further been confirmed in the DIAdvisor2 trial.

Overall the DIAdvisor presents a prediction quality on par with the best individual predictor. In some cases it even improves the predictive quality beyond any of the individual contributors. The Kernel-based predictor provides the best individual predictive result for a majority (20 min: 74%, 40 min: 63 %, 60min: 63 %) of all evaluated patients (DIAdvisor2). However, merging it with the other predictors in the integrator produces a DIAdvisor prediction that, for a significant amount of patients (20 min: 40%, 40 min: 44 %, 60min: 37 %), improves the predictive performance. Furthermore, the implemented integrator concept improves robustness against sensor disturbances or other data-related problems, algorithmic imperfections and programming errors causing temporary or permanent predictor drop outs. The integrator module only requires one functioning predictor at any instance, and constantly monitors the individual predictors' performances for immediate cut off in the case of out-of-bounds predictions. This feature maximised the availability of the DIAdvisor predictor to 93.8 % (Kernel Predictor: 92.7 %, State Space Predictor: 78 %, NARX Predictor: 88 %) of the time when a CGM signal was available.

4.2.3 Evaluation in simulation

An improved version of the integrator concept, taking advantage of prior information of individual predictor performance on given training data, was developed and verified using DIAdvisor1B and 1C trial data (12 patient visits). The simulation analysis indicates that the augmented algorithm improves the predictive performance even further, coming closer to the best predictor, as outlined in [5]. Moreover, the predictors and model make sense from a physiologic point of view, as shown in Figure 7 an intake of carbohydrate results in a physiologically plausible increase in blood glucose, while an insulin dose have a lowering effect on blood glucose.

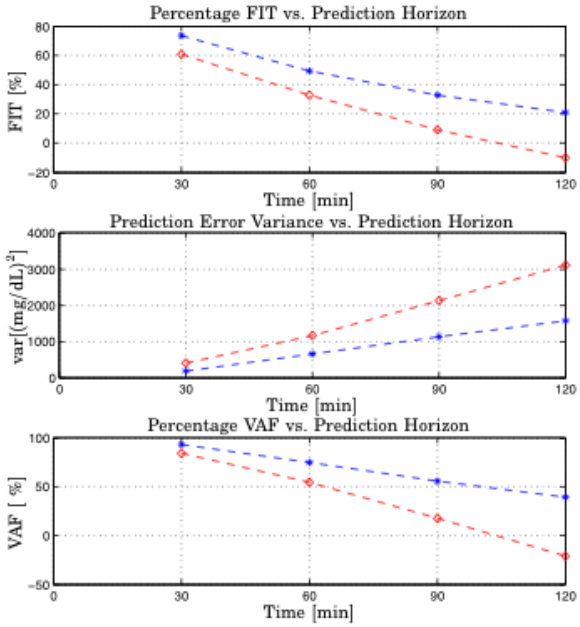

Figure 8: Patient CHU0102.. ARMAX-based predictor (blue star) vs. ZOH (red diamond).

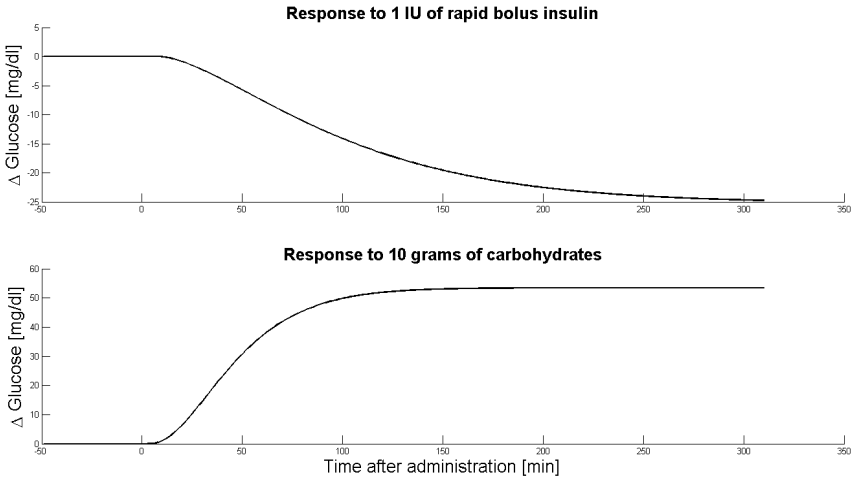

Figure 9: Example of BG response to 1 [IU] (top); BG response to 10 [g] carbohydrate (bottom)

4.2.4 Conclusions

The DIAdvisor model-based prediction has produced a methodology for development of patient-specific models and predictors. In summary, the following results were achieved:

- Three independent prediction algorithms were implemented into the DIAdvisor platform.
- A novel method for recursive Bayesian merging of multiple predictors was developed;
- Performance analysis show that the DIAdvisor prediction concept maintains a high availability, even in the case of individual predictor drop-outs, and that the prediction is in par with the best individual predictor, and in some cases improves the results further.

4.2.5 Outlook

The data collected in the DIAdvisor project are very rich and encourage more in-depth analysis.
From a prediction integration viewpoint further research is needed to investigate if, and how, the different predictors are specialised in different operating settings. Following this direction, the merging algorithm can be further developed into an unsupervised algorithm – making it more autonomous to learn these statistical relationships in an online setting.

4.2.6 References

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4.3 Work Package 3 – Predictive Control and Advisory System

Harald Kirchsteiger, University of Linz, including NNAS, JKU, ULUND, RICAM, RAMBOLL

4.3.1 Introduction

The task of WP3 is to develop a control system for BG control for Type 1 diabetic patients.

In a more detailed description, this task is to give advices on insulin quantity and time and also on additional carbohydrate corrections (quantity and time) to the patient. As a pre-requisite for this, continuous information flow from the patient through a CGM device is necessary.

Two essentially different paths were followed in the development of the controllers. On one hand there is a controller which follows the methodology of a Bolus Calculator, developed by partner NNAS. This approach only requires the estimation of insulin sensitivity and carbohydrate to insulin ratio for the specific patient to give accurate advices.

On the other hand, model-based control approaches were developed by partners ULUND and JKU which both work predictive. As those methods inherently rely on a model, the quality of the control system depends to a high degree on the quality of the mathematical model describing the glucose-insulin metabolism.

As a matter of fact, the model quality was identified as major bottleneck: accurate short time prediction models up to 20 minutes were developed in WP2, but long term predictions required for model predictive control in the range of 240 minutes or more [1] are highly unreliable or even unstable.

4.3.2 Design Methods

This section describes the three main control approaches developed. All of them were designed in such a way, that impulsive control actions are given, i.e. the controller is applicable for patients on multiple daily insulin injection therapy and does not necessarily require an insulin pump. One possibility to reach this was presented in [2].

Bolus Calculator (NNAS)
The bolus calculator computes the insulin advice based on

$$Insulin_{advice} = \frac{Carbs}{CIR} + \frac{BG_{current} - BG_{target}}{ISF} - IOB$$

and the carbohydrate advice based on

$$Carbs_{advice} = -\frac{BG_{current} - BG_{target}}{ISF} \cdot CIR$$

where *Carbs* is the carbohydrate content of the meal, $Bg_{current}$ is the currently measured BG concentration, BG_{target} is the desired target glucose concentration, *IOB* is the insulin on board, i.e. insulin still in the body from previous injections, *CIR* is the carbohydrate to insulin ratio and *ISF* is the insulin sensitivity factor.

Besides those formulas, some empirical rules were implemented in the controller, e.g. in clinical practice the time in-between two insulin injections should be approximately 120 min.

The Bolus Calculator based controller was tested in the DIAdvsior1 and DIAdvisro2 clinical trial with convincing results. This is further described in Section 4.5

Optimisation Based Control (ULUND)
This control approach solves a nonlinear optimisation problem to determine the optimal insulin and carbohydrate correction advices in the sense of a certain cost function. The results of such an optimisation depend to a large extent on two ingredients: the optimisation function and the mathematical model utilised to simulate the patient behaviour when searching for the optimal advices. Here, an asymmetric cost function is implemented, penalising deviations from a given set-point into direction of hypoglycaemia much more than deviations into direction of hyperglycaemia.

The internal model of the controller is based on an approximation of the glucose responses to insulin and carbohydrates through gamma functions [3].

The optimisation of the cost function

$$\min_{u_i,u_g,t_i,t_g} \sum_{i=1}^{H_p} 10^{-3}\left(y\left(u_i,u_g,t_i,t_g,t\right)-y_{ref}\right)^2\left(c_1+30c_2e^{-0.05y\left(u_i,u_g,t_i,t_g,t\right)}\right)$$
$$s.t. \quad u_i<20, u_g<80, y_L\le y\le y_U$$

is done online at every sample time and yields the optimum time and amount of insulin (t_i, u_i) and carbohydrate corrections (t_g, u_g) respectively, dependent on the shape of the cost function which is defined by the parameters c_1 and c_2 and the predicted glucose $y\left(u_i,u_g,t_i,t_g\right)$ with the internal model, subject to input and output constraints.

Model Predictive Control (JKU)
Similar to the optimisation based controller, also the model predictive controller (MPC) requires the definition of a cost function which will be minimised and a model of the process. System identification methods were used to determine a linear model which makes use of carbohydrate and fast acting insulin bolus inputs to simulate glucose responses. Consequently, the linear MPC solves an optimisation problem in the form of a quadratic problem

$$\min_x \frac{1}{2}x^THx+f^Tx, \quad s.t. \quad A_cx\le b_c$$

subject to constraints at every sample time. Here, the Hessian *H* and the gradient *f* are defined by the mathematical model of the patient. Such kind of optimisation problems are convex and have a unique optimum and can be solved efficiently using well established methods.

Input constraints were imposed to limit the insulin doses to a lower level of zero, however output constraints were avoided to circumvent the risk of infeasibility problems in the presence of model-plant mismatches. Instead, an asymmetric weighting functionality was developed [4] which can be tuned in such a way that dangerously low and high blood glucose values are avoided.

4.3.3 Control Verification in a Simulation Environment

The three control algorithms described in the previous section were evaluated on a simulation model of a diabetic patient developed in WP1. Figure 10 gives an overview of the control structure.

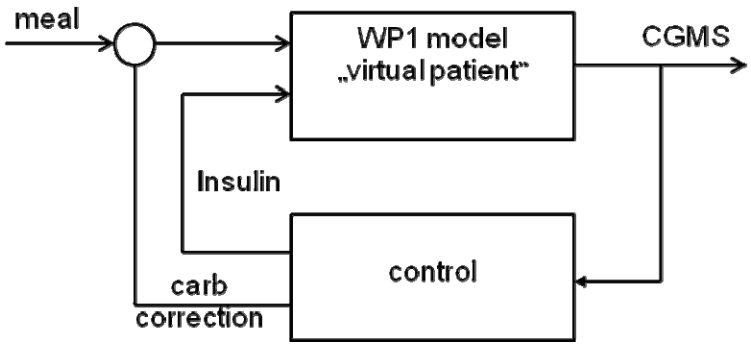

Figure 10: Schematic overview of the controller simulation environment

In total, 3 parameter sets of the simulation model representing 3 different virtual patients were used to test the developed controllers. As simulation scenario, a 3 day period with 3 meals per day at nominal time {8.00, 13.00, 19.00} and quantity {40, 80, 60} g carbohydrates was used. Both quantities and times were varied randomly by ±1h and ±20g, respectively.

The results are evaluated using several performance metrics:

- Low Blood Glucose Index (LBGI), High Blood Glucose Index (HBGI), [5]
- Total time spent in safe range (70-180 mg/dl)
- Total amount of insulin advices per day (in insulin units)
- Number of insulin advices per day
- Total amount of carbohydrate advices per day (in grams)
- Number of carbohydrate advices per day

The following Figure 11, Figure 12 and Figure 13 show results for the virtual patient number 1. Performance metrics for all virtual patients are summarised in Table 3. In the clinical trials, the Bolus Calculator was implemented in the DIAdvisor system whereas the other controllers were only tested in simulation.

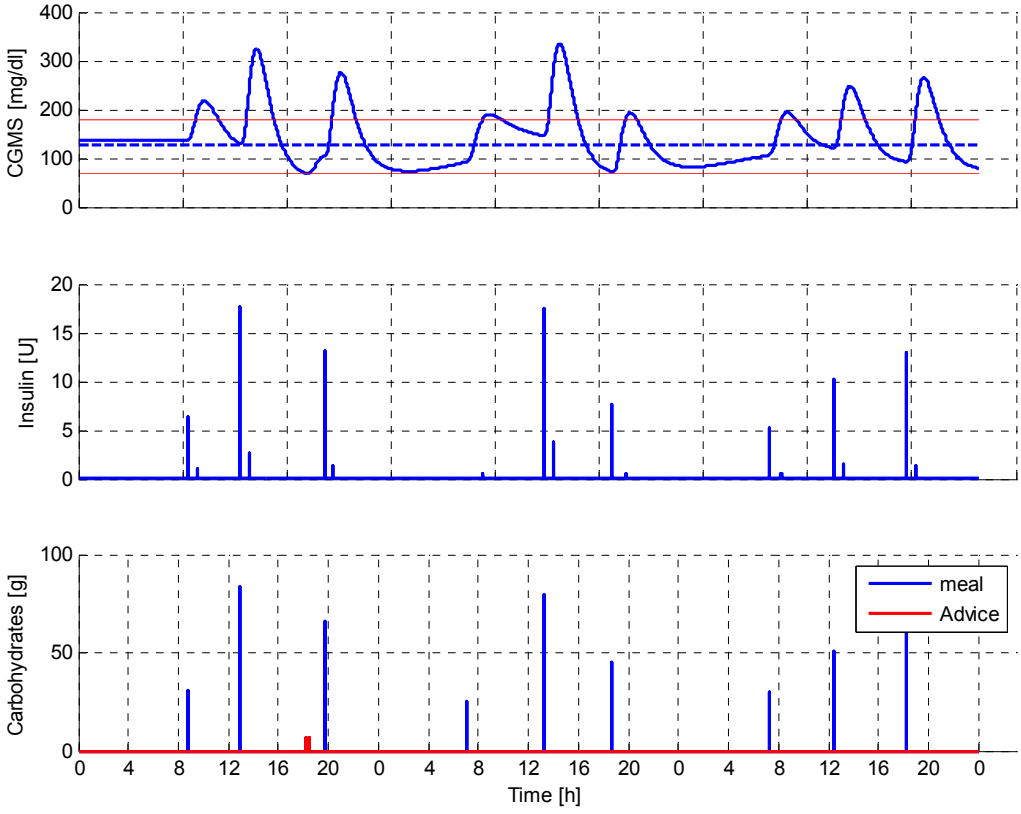

Figure 11: Bolus Calculator (NNAS)

Figure 12: Optimisation based control (ULUND)

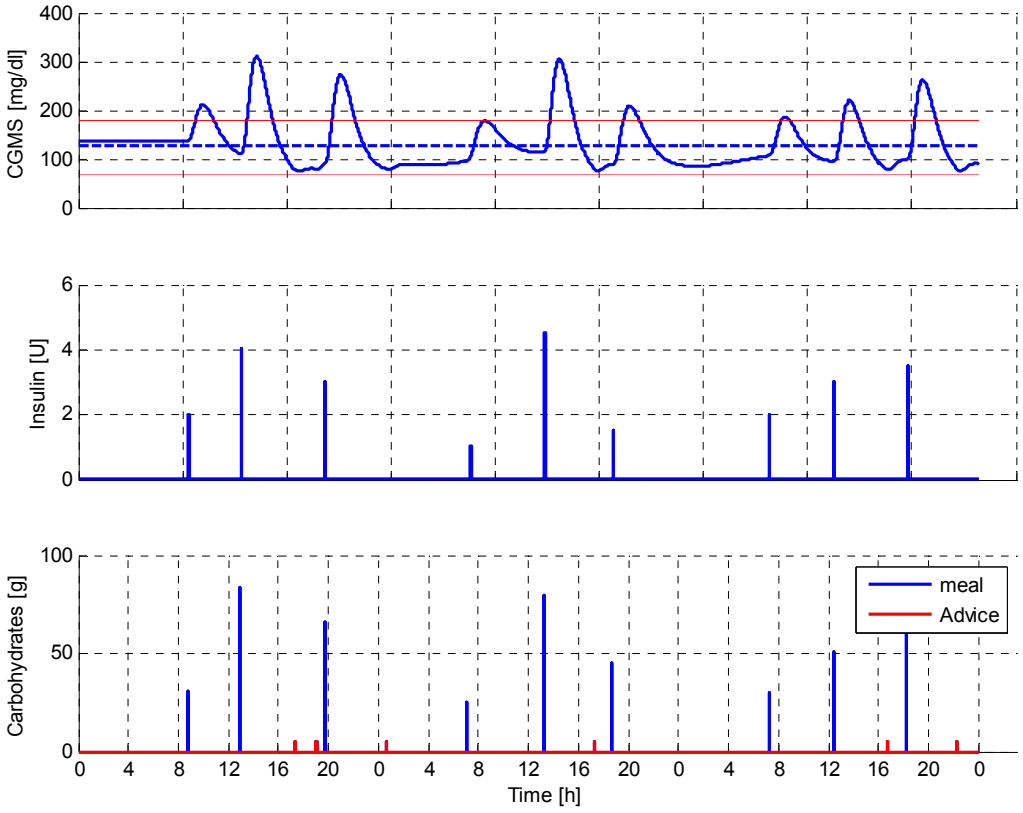

Figure 13: Model Predictive Control (JKU)

	LBGI	HBGI	Tsafe[min]	Tsafe[%]	Tot.daily Insulin	InsulinAdv per day	Tot.daily Carbs	CarbAdv per day
NNAS	0,9748	4,9806	3346	77,44	34,7	5,7	4,7	0,7
ULUND	0,1587	8,7870	2699	62,46	32,8	1,7	33,5	2,3
JKU	0,8370	3,8785	3586	82,99	40,8	3,0	10,0	2,0

Table 3: performance metrics for the 3 controllers

4.3.4 Conclusion

Both model-based controllers and a Bolus Calculator based controller, which does not rely on the separate task of finding a model of the glucose insulin system, were developed and tested in simulation. The simulation results show the good performance in regulating blood glucose and avoiding dangerously low BG concentrations. Those results are however not directly applicable to real patients as there is the need for an accurate, patient specific mathematical model.

Further the Bolus Calculator based controller was tested in clinical trials with convincing results (see section 4.5).

4.3.5 References

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4.4 Work Package 4 – DIAdvisor Device Platform and Realisation

Dr. Alison Burdett, Director of Technology, Toumaz Technology Ltd including NNAS, TOUMAZ, INT, ONDALYS, RMS, RAMBOLL, IDF

4.4.1 Objectives of WP4

The objective of WP4 was to design and develop the device platforms (software, hardware and sensors), to enable the DIAdvisor system to be used and tested in clinical trials. Following this objective, the WP4 team had to resolve and find the appropriate solution for several technical challenges:

- System architecture: there are several partners who implement different tasks using different technologies. Some tasks like data modelling and simulation are implemented using the specialised technologies like Matlab, other tasks are implemented into C# language.
- Create a friendly user interface making the system to be easy to use and adapted to the patients who have no knowledge in informatics systems.
- Collect all clinical data, save into local database and synchronise the patient database with the central database
- Data presentation, analysis and exportation

Below is presented the solution adopted for these challenges and the obtained results.

4.4.2 The system architecture

The system overview given in Figure 14 below highlights the main functionality of the system:

- The patient uses an Ultra Mobile PC (UMPC) connected to the sensors (DexCom which measures the blood glucose and Sensium which gives the heart rate and acceleration).
- The UMPC sends all information to the clinician laptop using a Wireless Access Point. The clinician analyses the data and validates the advices raised by the UMPC to be displayed to the patient.
- All data for all patients is uploaded to a FTP server and is available for post analysis.

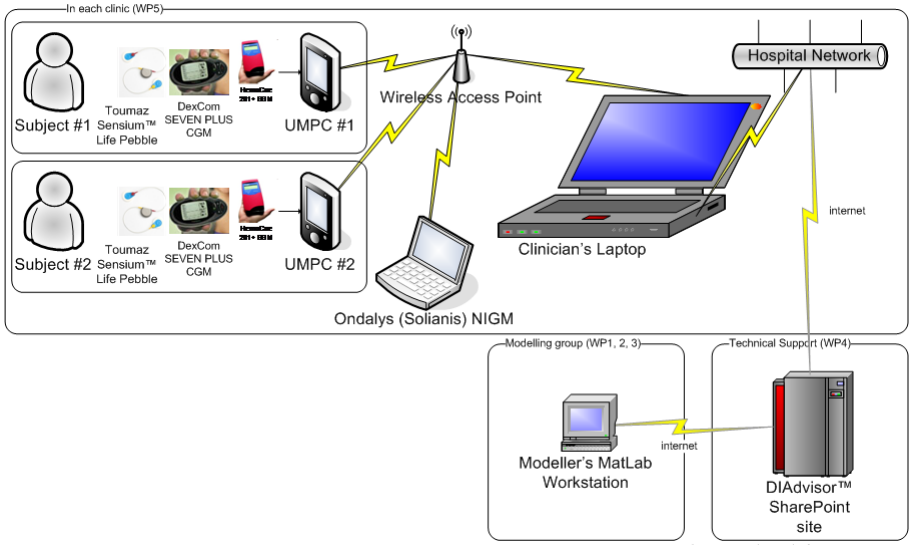

Figure 14: System Overview

The software architecture has to be flexible enough in order to be able to incorporate modules built on different technologies by different partners, and also these modules should not be coupled too tight. Each partner should develop his software module, test the functionality and then include into the system architecture. For this reason, the *Service Oriented Architecture* (SOA,

http://en.wikipedia.org/wiki/Service-oriented_architecture) combined with the *Agile* project planning philosophy (http://en.wikipedia.org/wiki/Agile_software_development) was adopted.

There are several distinct software modules according with the main tasks that the system should implement:

- Sensor Input: connects and reads from the sensors the measured data.
- Local Decision Engine: calculates the blood glucose prediction, gives advices for treatment improvement.
- Data Store: stores the all collected data, send this data to the central server which collects the data for all patients
- Man Machine Interface: the interface with the patient, displays the data, read the patient's inputs.
- Clinician Application: display and analyse the clinical data, advice validation, data exporting for post analysis.

The system block diagram showing the main software modules (organised as services) and the interaction between these services is given in Figure 15 below:

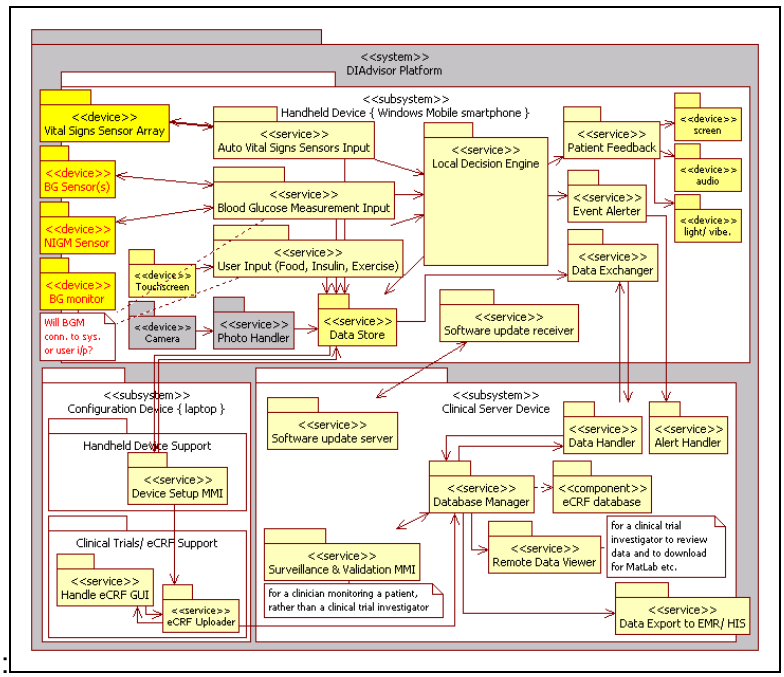

Figure 15: System Block diagram

This is a *service oriented architecture (SOA)* in which each subsystem is modelled as a set of inter-related *services*. Each service has a formal interface specification and a formal test plan to facilitate independent development of each service but with defined integration milestones.
A key element of the architectural concept of the DIAdvisor handheld device software is to use a 'controller assembly' to apply Dependency Injection (http://en.wikipedia.org/wiki/Dependency_injection) and thus conform to the Dependency Inversion Principle:

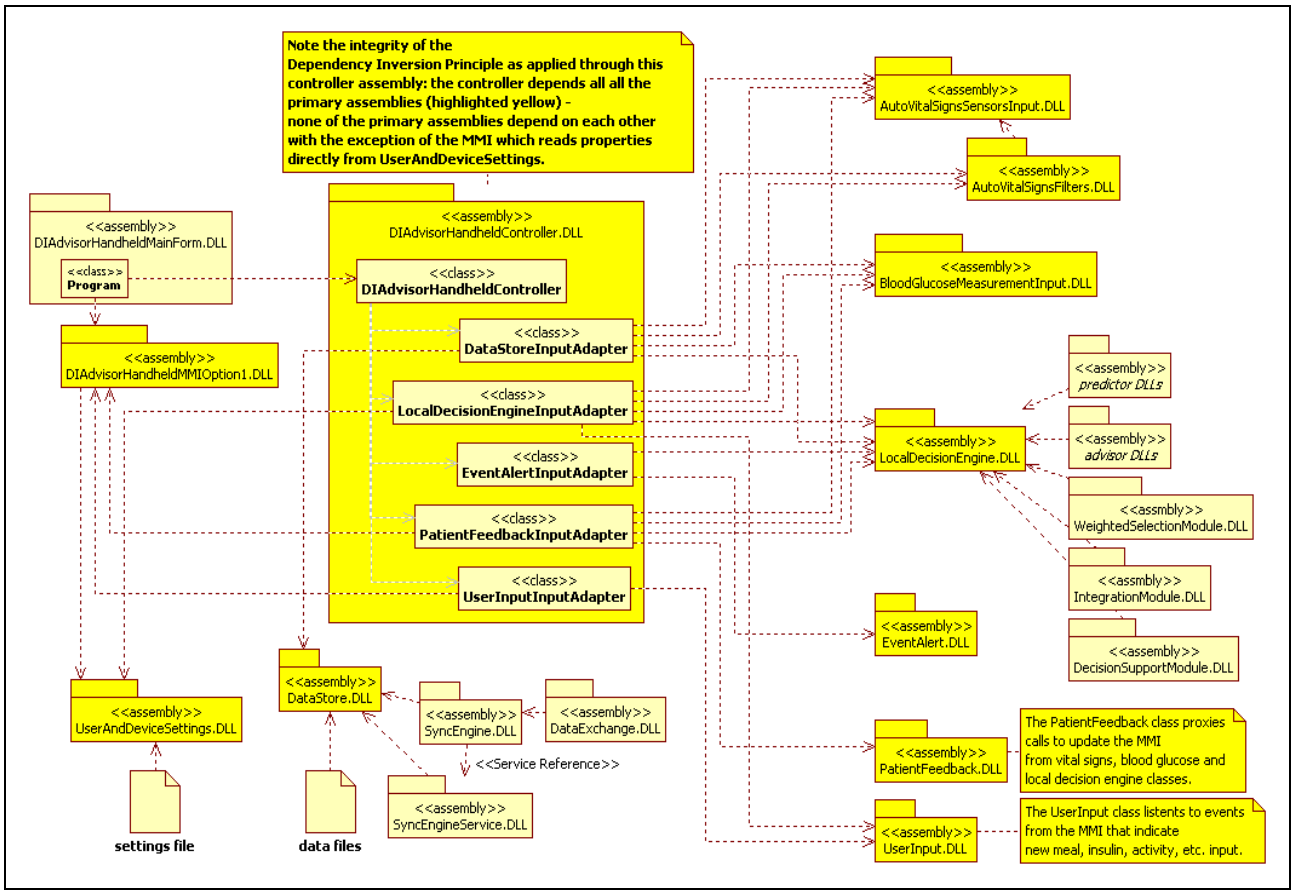

Figure 16: Handheld Device – application of Dependency Inversion Principle

4.4.3 Graphic User Interface

Data visualisation represents an important task of the project because the quality of the Graphic User Interface (GUI) could make the user to accept or reject the entire system. Even if the system provides very good advices and is very useful for the patient, a poor user interface could lead the subject abandoning the system. In order to implement a high quality GUI, we have used the Windows Presentation Foundation (WPF) technology. WPF attempts to provide a consistent programming model for building applications and provides a separation between the user interface and the business logic. Programmers do not have the skills necessary to build friendly graphical objects, these skills belong to graphic designers, but the designers cannot write software code. The WPF resolves this issue giving designers the tools to develop graphical objects using the appropriate design tool and, after that, the programmers add code to make those objects respond to the user actions. This unification is possible by using the Extensible Application Markup Language (XAML) which is a user interface markup language to define UI elements, data binding, eventing, and other features. XAML files can be created and edited by the designers with visual design tools like Microsoft Expression Blend, Vector Architect and then customised by the programmers using the Microsoft Visual Studio.

An example of the user interface displayed by the two main software applications (Patient Application Figure 17 and Clinician Application Figure 18) is given below:

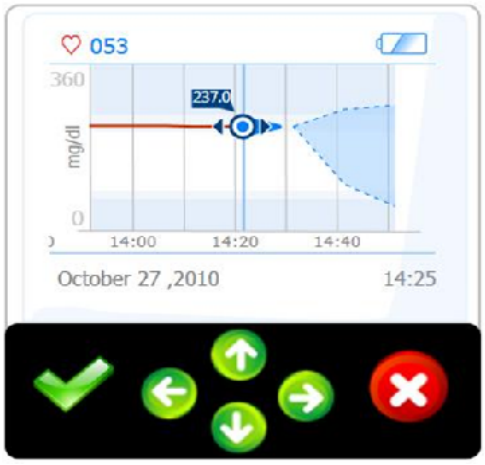

Figure 17: User interface of the Patient Application

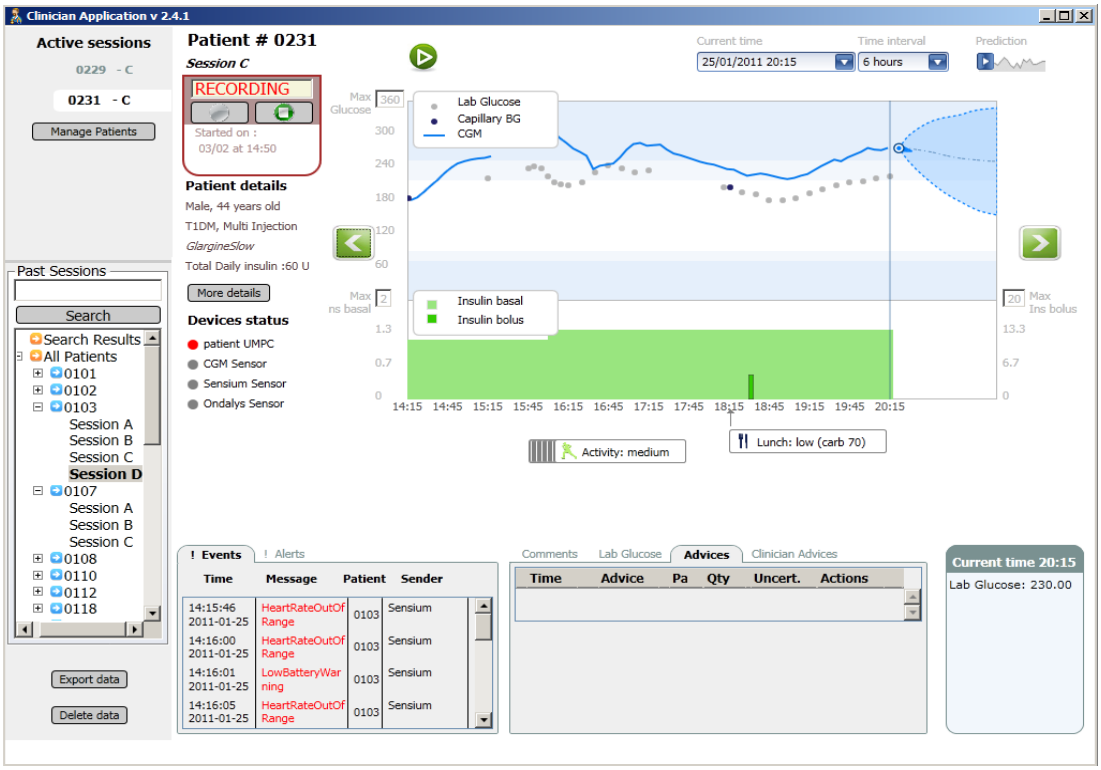

Figure 18: User interface of the Clinician Application

4.4.4 Conclusions

DIAdvisor platforms designing process has raised a series of issues due to the system complexity, the number of partners and involved technologies, the flexibility and quality imposed for the user interface. All encountered issues have been successfully resolved by using the most advanced techniques for designing and developing software, and the latest technologies on data presentation and data transmission.

The learnings made through development of the DIAdvisor system and testing it clinically, has been condensed into a first draft specification for a commercial system.

4.5 Work Package 5 – Clinical Tests and Assessment

Prof. Eric Renard, University of Montpellier including CHU, UNIPD-DMCS and IKEM

4.5.1 Introduction

In the 4th year of the project, the DIAdvisor1 trial has been finalised. Success criteria have been reached in terms of data collection in the DIAdvisor system, glucose prediction at a 20-min horizon and therapeutic advices given by the system. These successes have been reached in the controlled setting of a Clinical Research Centre (CRC) where the patient moved minimally and took standardised meals. Ultimate steps of DIAdvisor1 trial allowed the testing of the system in challenging conditions: exercise, large meal size, provocative hypo- and hyperglycaemia. Success criteria were also reached in these conditions. The data from DIAdvisor1 trial have been accepted for presentation at the meeting of European Association for the Study of Diabetes in Berlin, October 2012. A paper reporting these data is scheduled to be submitted in the journal Diabetes Care in the followings.

DIAdvisor2 trial has been performed and achieved in 58 patients during the 4th year. The preliminary analyses of the study results indicate the highly significant benefit of using DIAdvisor in the reduction of time spent in hypoglycaemia and a marginally significant benefit in the improvement of time spent in the near-normal targeted glucose range. These positive achievements in a CRC setting support the interest of investigating DIAdvisor use in home conditions and in a larger patient population.

4.5.2 Provide clinical data for WP1, WP2, WP3

From the early beginning of DIAdvisor project, the protocol for collection of large amounts of clinical data from diabetic patients has been prepared between the clinical sites involved in WP5, as well as between CHU as WP5 leader and WP1, 2 and 3 leaders and their research teams. Preparation of the platform for data recording has been performed in tight collaboration with Toumaz and RomSoft. Thirty diabetic patients (25 Type 1 and 5 insulin-treated Type 2) have been recruited as volunteers for participation in the Data Acquisition trial (DAQ trial) at each clinical site. Participating subjects have been recruited and investigated at each clinical site in accordance with ethical regulations. Briefly, patients were recruited according to their fulfilment of inclusion criteria and no exclusion criteria.

An initial 3-day period was spent in the Clinical Research Centre where the patients underwent repeated blood sampling for glucose and insulin assays, measured capillary glucose using HemoCue meter according to a timely schedule, wore a continuous glucose monitoring system (Navigator, Abbott) and a LifeShirt for vital sign recordings (Vivometrics) and had their blood glucose estimated by the non-invasive Ondalys device (this last procedure at CHU only). Standardised meals were given to the patients three times daily, including deuterated glucose at breakfast. During a secondary 7-day period, the patients measured capillary glucose using HemoCue meter according to a timely schedule and wearing the Navigator system and the Lifeshirt. Finally, in hospital, the patients performed a standardised exercise sequence while repeated blood sampling was done for blood glucose and plasma insulin assays, together with wearing the Navigator system and the Lifeshirt and testing the non-invasive Ondalys device (this

last procedure at CHU only). Gathered data have been collected in a central registry to be used by WP1, 2 and 3 participating partners.

4.5.3 First DIAdvisor in-vivo test

In order to develop a short-term predictor of blood glucose concentration, the numerous data collected in DAQ trial have been analysed by WP1, 2 and 3 specialised in mathematics and data modelling. Based on past and real-time data given by CGM sensors, but also meal and insulin delivery information, the produced algorithms were supposed to provide blood glucose predictions up to two hours. It has been combined with an advisor engine which aims at providing advice to adapt patient therapy. The prediction and advisor engines have been integrated into a user-friendly interface so that the patient could easily interact with the algorithms. This new system can be defined as the first prototype of a “mobile short-term blood glucose predictor and treatment advisor”.

In order to test the user interface, as well as the prediction and the advisor engines developed by the DIAdvisor consortium, a protocol was designed according to a step by step approach: a step did not start before primary end-point of the previous one has been fulfilled. It allowed an evaluation of each part of the system separately. The testing process included three main steps as listed below:

A. Testing of Data Collection
B. Testing of Blood Glucose Prediction
C. Testing of Therapy Advices

Three additional steps were conducted as extension studies to provide further information about the system performance under specific conditions:

D. Testing of Prediction and Therapy Advices during physical activity
E. Testing of Prediction and Therapy Advices in case of large meals
F. Testing of Prediction and Therapy Advices in induced hyper- and hypoglycaemic conditions

The objectives (primary endpoints) were defined for each step:

1. Step A: The system can accurately and easily collect data coming from patient inputs and the continuous glucose monitoring device by more than 80% of time of use.
2. Step B: The system provides at least 80% accurate and > 95% safe glucose predictions at time + 20 min, i.e., if following criteria are reached: % paired glucose trends (predicted glucose t to t+20min / real glucose t to t+20min) in A & B zones of CG-EGA > 80% (accuracy) AND <5% in E zone of CG-EGA (safety) when glucose t is within 70-180 mg/dl range.
3. Step C: Coherence between system advices and physician recommendations is >0.80 for grade A advices (coherent, not coherent, harmful, very harmful). ‘Coherent’ is defined as advice suggesting an intervention in the same direction, ‘Non coherent’ as advice suggesting interventions in opposite directions, ‘Harmful’ as system advice in opposite direction to physician advice and that would result in hyper- or hypoglycaemia (>180 or <70 mg/dl, respectively) within 20 minutes, ‘Very Harmful’ as system advice in opposite direction to physician advice and that would result in hyper- or hypoglycaemia (>180 or <70 mg/dl, respectively) within 10 minutes. The extension studies dedicated to physical exercise, large meals and hyper-/hypoglycaemic conditions were considered as successful if:
4. Steps D, E, F: The system provides at least 80% accurate glucose predictions and coherent advices in tested conditions, also including > 95% safety.

Task 5.2 was achieved as scheduled with success in reaching predefined criteria at all steps. Of note, prediction accuracy was finally assessed using the point Clarke Error Grid analysis by using YSI reference glucose measurements instead of CG-EGA because of the limited accuracy of the CGM system (Dexcom Seven Plus).

4.5.4 Second DIAdvisor in-vivo test

From the success obtained in DIAdvisor1 trial, a DIAdvisor2 trial has been designed as a phase-2 clinical trial in order to assess in a CRC environment the benefits on glucose control by using prediction and advisory information from DIAdvisor system vs. common management of insulin therapy from capillary glucose measurements and usual education rules.

Main objective:
To evaluate the efficacy in keeping blood glucose in a safe range (70-180 mg/dl) of the second generation of a Glucose Predictive and Therapy Advisory system (DIAdvisor2) in diabetic patients treated by basal-bolus insulin regimens using pumps or multiple daily injections. A clinically significant benefit will be reached if an increase of at least 10% of time in range is obtained while using DIAdvisor2.

Secondary objectives:
To assess

- hypoglycaemia (<70 mg/dl) while using DIAdvisor2
- hyperglycaemia (>180 mg/dl) while using DIAdvisor2
- the effect of DIAdvisor-2 on mean blood glucose.
- the accuracy of glucose prediction by DIAdvisor2
- the coherence of therapy advising by DIAdvisor2

Ancillary objectives:
To collect information from

- non-invasive glucose monitoring as a potential substitute for continuous glucose monitoring.
- vital sign sensing as a potential tool for improved glucose prediction and therapy advisor.

Study design:
This is a randomised controlled crossover trial. Due to the use of different devices during compared periods, this study cannot be blinded. It includes a preliminary 4-week run-in period to allow a learning phase for CGM use. A meal-test in CRC is performed during the run-in period for personalised modelling purpose.
Patients are then admitted for two inpatient visits of 3 days in a CRC, one with DIAdvisor-2 (interventional period) and one without (control period). The two admissions are performed 1 to 4 weeks apart. Patient continues using CGM device in-between.
Patient datasets will be eligible for statistical analysis only if more than 70% of expected data per patient are collected by the platform and if patient follows more than 70% of advices suggested by the DIAdvisor system.

Number of subjects:
50 as calculated in view of a 10% difference of primary endpoint between interventional and control periods with a power >0.90 and an error < 0.05, to be expanded to 60 in case of failures of patients to perform both study periods or in case of ineligible datasets.
20 patients are expected to be investigated in each of the 3 clinical centres (CHU, UNIPD, IKEM).

Study performance:
The study protocol has been approved by Ethical boards at CHU, IKEM and UNIPD in 2011.
The investigations have been performed at:

- CHU in 17 patients. Three other patients were included but failed in achieving the 2 investigational periods.
- IKEM in 23 patients. Two other patients were included but failed in achieving the 2 investigational periods.
- UNIPD in 17 patients. Two other patients were included but failed in achieving the 2 investigational periods.

A total of 57 patients could finally achieve the study protocol and provide exploitable data.

The characteristics of the patients who achieved the trial are the following:

- Age: 39 +/- 13 years
- Gender: 77% males (n = 44)
- All with Type 1 diabetes mellitus
- Treated by insulin pumps (n = 30; 53%) or multiple daily insulin injections (n = 27; 47%)

All study data coming from the three investigation centres were gathered in a central data base.
Ancillary objectives of the trial could not be achieved due to the lack of sustained stability of vital sign capture during the early steps of the trial and the insufficient accuracy of the non-invasive Ondalys device to allow clinical use.

As scheduled in the trial protocol, individual data had to be reviewed before analysis in order to identify the patients who fulfilled the criteria of at least 70% collected glucose data (CGM and YSI-measured) and at least 70% followed advices while using DIAdvisor system.

It turned out only 31 patients were classified as 'fully compliant' since they could satisfy the predefined criteria allowing data analysis. 12 patients had more than 70% glucose data available but followed slightly less than 70% advices; they were kept for the analysis since classified as 'compliant'. Nine patients had 50-70% expected glucose data and 5 patients did not reach the 50% threshold on expected glucose data. So, 13 patients had to be discarded for the analysis of the study outcomes, whereas 43 patients could be eligible for this analysis.

Data analyses:
WP1 partners proposed a method to merge the clinically useful information obtained from the two types of glucose measurements, i.e. high accuracy of reference YSI-measured BG and high spatial resolution of CGM. The method checks for data consistency (outlier detection on both CGM and YSI data), compensates for CGM drift in time due to changes in sensor sensitivity and measurement noise, exploiting YSI reference measurements. The output of the method is a retrofitted CGM profile, i.e. a frequently (and uniformly) sampled glucose time series where the dynamics recorded by the CGM are used to smartly interpolate among two/more different YSI. Depending on user needs, the retrofitted CGM profile can be provided at any time sampling, e.g. once every minute or once every 5 minutes.
The method has been recently filed for patenting. Once the patenting process will be completed, details on the method will be made available on a scientific publication.

Primary study outcome is the % time of blood glucose in near-normal range (70-180 mg/dl).
Secondary outcomes include: % time of BG below the near-normal range (<70 mg/dl), % time of BG above the near-normal range (>180 mg/dl), mean BG level.

The results computed in the 43 patients eligible for data analysis is presented in Table 4 below.

	DIAdvisor	Control	Difference	p-value
Percent time in near-normal range	67,89	63,07	4,82	**0,05**
Percent time in hypoglycaemia	2,44	4,17	-1,73	**0,01**
Percent time in hyperglycaemia	29,67	32,75	-3,08	0,21
Mean Blood Glucose (mg/dl)	156,55	157,23	-0,68	0,77

Table 4: Primary study outcome in the 43 patients eligible for data analysis

As presented above, the % time in the near-normal range was significantly increased (p=0.05, Wilcoxon signed rank test). The difference of % time below 70 mg/dl was highly significant (p=0.01) in favour of DIAdvisor use. Percent of time above 180 mg/dl and mean blood glucose levels were similar with or without DIAdvisor use.

In other words, the % time in near-normoglycaemia was increased by 7.6% and the % time below 70 mg/dl was reduced by 42% while DIAdvisor was used.
Interestingly, the benefit of DIAdvisor use was also significant in terms of % time below 70 mg/dl (hypo) in the whole patient population (n=57), i.e. also including non-compliant patients. Data analysis performed in the whole population is shown in Table 5 below.

	DIAdvisor	Control	Difference	p-value
Percent time in near-normal range	67,19	63,71	3,48	0,10
Percent time in hypoglycaemia	2,55	4,31	-1,76	**0,00**
Percent time in hyperglycaemia	30,26	31,98	-1,72	0,37
Mean Blood Glucose (mg/dl)	156,93	155,82	1,11	0,89

Table 5: Primary study outcome in the whole patient population (n=57), i.e. including non-compliant patients

Comments:
In agreement with DIAdvisor1 trial, the present study demonstrates that DIAdvisor is able to collect patient inputs and CGM data as well as to provide advices to help the patients to adjust their therapy in view of keeping blood glucose closer to normoglycaemia. This supports the feasibility of the concept and the usability of the device.

Moreover, our results demonstrate that using DIAdvisor with a good compliance to DIAdvisor advices allows the diabetic patients treated by basal-bolus insulin therapy to improve the time they spend in near-normoglycaemia and, more significantly, to reduce the time spent in hypoglycaemia.
Although it did not reach the statistical significance, the time spent in hyperglycaemia (above 180 mg/dl) tends to be reduced while using the DIAdvisor.
Overall, the mean blood glucose is not significantly affected by the use of DIAdvisor.

According to the clinician view, these results argue in favour of improvements of safety and glucose variability associated with DIAdvisor use while no clear benefit can be found in terms of overall glucose control. Of note, most included patients showed rather well-controlled diabetes as shown by the mean blood glucose levels during the control experiment; hence, a significant improvement of this parameter was hard to achieve during DIAdvisor use.

Most sophisticated approaches of automated insulin delivery using closed-loop algorithms based upon blood glucose levels and their predictive evolution lead to similar results, i.e. a reduction of hypoglycaemic occurrences and lowered blood glucose variability while average blood glucose level remains almost unchanged.

The value of such results is well graded by the patients who mostly fear hypoglycaemia and have their quality of life severely impaired by blood glucose variations.

Better outcomes would be expected from a significant reduction of blood glucose excursions above normal range. These glucose spikes usually occur after meals and in stress conditions. The current clinical version of DIAdvisor poorly addressed these destabilizing conditions since the short-term prediction of blood glucose evolution, per se validated as accurate, was not yet ready to be used by the clinical advisory (control) algorithm. Moreover, due to the lack of reliable vital sign sensing device during the project, indices of stress like heart rate have neither been integrated in the advisory algorithm. One may expect that integrating the glucose prediction and the vital sign signals could allow prospective advices which would anticipate high blood glucose deviations, hence lead to lower average blood glucose values.

These comments pave the way toward further developments of the DIAdvisor approach:

- by assessing the usefulness of the current device in real life, outside the hospital environment , in patients who would be first taught to the use of DIAdvisor and who would be equipped by a more portable version of the tool..
- by upgrading the current DIAdvisor version thanks to the integration of glucose prediction algorithms in connection with the advisory algorithm, and as soon as available the addition of inputs from vital sign sensing devices.

The non-invasive glucose sensing approach will request further development efforts before being usable thanks to a clearer reliability.

The extension of use of DIAdvisor to patients using non basal-bolus insulin therapy or to type 2 diabetic patients is currently not expectable due to the limits of the current device.

4.5.5 Conclusion

From the project clinical data, the DIAdvisor concept has been validated.

Beside the feasibility of data capture, glucose prediction on short-term horizon and patient advising on treatment adjustments, DIAdvisor use in a controlled environment has shown, through a randomized control trial, significant improvements in glucose control in terms of occurrence of hypoglycaemia and excursions out of targeted range. The reduction of blood glucose variability is perceived as a very valuable outcome since it improves patients' quality of life and reduces their fear for hypoglycaemia which usually prevents them in adjusting their insulin therapy as needed.

The benefit of reducing blood glucose variability on longer-term diabetes-related complications is still a non-answered question. Investigational data have shown a deleterious impact of glucose excursions on oxidative stress and vascular relaxation. Blood glucose variability has also been correlated with HbA1c levels in diabetic patients treated by multiple daily injections. Hence, DIAdvisor could be a promising tool that could contribute to a better diabetes prognosis on long-term.

Further development should include a more user-friendly portable platform such as a small tablet PC connected to the CGM system. Besides, a training program for patient use should be built

based on a simulation station which allows the patient to be trained in providing manual inputs on insulin doses, meal intakes, physical exercise and blood glucose measurements for CGM calibration, and understanding of given glucose prediction and advices. The way of managing this information in order to improve glucose control should also been taught.

Next expected trials should be designed in view of the demonstration of better glucose control while using the DIAdvisor system in everyday life as outpatient. The DIAdvisor system could then be considered as a complementary device to combined CGM and insulin pump therapy. Possible use in patients wearing CGM and treated by multiple daily insulin injections has also to be investigated

5. Potential Impact

5.1 Contribution to improve diabetes control and outcomes

Providing diabetic patients with a unique tool to help better manage their disease in terms of effectiveness as well as in terms of safety and quality of life, DIAdvisor has shown in clinical trials that it is possible to minimize time spent in hyperglycaemia, increase the time in normal range and decrease the time in hyperglycaemia.

Extending this to longer periods, this result can be translated to an overall better control in terms of fewer short term complications caused by hypoglycaemia and fewer long term complications caused by hyperglycaemia. Again this can be translated into better treatment outcomes, reduced complications [17] [18] and eventually an improved quality of life and reduced health costs.

Concomitant prediction of hypoglycaemic risk will both contribute to a more confident and effective adaptation of insulin doses and to a reduction of severe events that may endanger immediate life and require emergency hospital admissions.

A predictive tool in itself could dramatically change everyday life for numerous diabetic patients. While direct benefits in terms of quality of life would be rapidly expected, indirect benefits in terms of professional perspectives should also ensue. Moreover, immediate advice provided by the tool software and optionally complementary counselling provided by the health care provider connected to the personal data should alter the current conditions of life of most diabetic patients who at present are alone in deciding, based on their personal experience how to modulate their therapy.

Efficiency in diabetes management due to the not increased burden on patient and health care provider should be a valuable benefit of the proposed approach.

5.2 Contribution to stabilisation of the costs of the health care systems

Recalling that the CODE-2 study[19] performed in eight European countries reported that

- Type 2 diabetes mellitus (representing > 90% of diabetic cases) was responsible for 1.6-6.6% of total healthcare expenditures per country.
- In 1999, around €29 billion were spent in these countries for direct medical costs related to diabetes, i.e., a yearly estimated cost of €2.834 per patient.
- Of interest, 55% of these expenses were due to hospitalizations related to diabetes.
- Moreover, the CODEIRE study[20] performed in Ireland reported that a diabetic patient affected by microvascular or macrovascular complications was responsible for a cost 1.8 or 2.9 times that of a non-complicated patient, respectively. Average cost related to a patient affected by both types of complications reached 3.8 times that of a non-complicated patient.
- 20 million people in the EU have diabetes

[17] UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with Type 2 diabetes (UKPDS 33). The Lancet 1998, 352 : 837-53.
[18] The Diabetes Control and Complications Trial Research Group.The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329, 977-86.
[19] Jönsson B on behalf of CODE-2 Advisory Board. Revealing the cost of Type II diabetes in Europe. Diabetologia 2002, 45: S5-S12.
[20] Nolan JJ, O'Halloran D, Mc Kenna TJ, Firth R, Redmond S. The cost of treating Type 2 diabetes (CODEIRE). Ir Med J 2006, 100: 307-10

- 40 million people in the EU have pre-diabetes
- Diabetes costs the EU €130 billion per year

From this data, hospitalisation costs and complication related expenses appear as the major burden of diabetes on health care systems. DIAdvisor use in hospitalised patients, notably in critical care units, should reduce time spent in hospital for major events such as myocardial infarctions, strokes or post-surgical follow-up, due to improved glucose control impact.

Everyday use of DIAdvisor in ambulatory patients should help in preventing both acute metabolic events that require hospitalisation and recurrent hospitalisation for poor diabetes control. Sustained lower levels of HbA1c represent the most efficient way to decrease emergence or impairment of complications that induce the most considerable expenses.

Foreseen costs related to education for use of the DIAdvisor, as well as maintenance of an advisory unit for DIAdvisor users, current expenses motivated by hospitalisations and complication care are in comparison considerably higher.

5.3 Improving quality and efficiency of healthcare

As demonstrated in the DIAdvisor clinical trials, the time spent in normal blood glucose range is increased, time in hyperglycaemia decreased and still time in hypoglycaemia is significantly decreased. Evidently a main effect of the DIAdvisor system can be to reduce the negative effects of hyperglycaemia and hypoglycaemia and therefore it will provide a reduction of the social costs of related complications.

As a measure of this is that a reduction of Hb1AC by 15% without increase of hypoglycaemia cases means a reduction by 10% of long-term complications[21] i.e. a corresponding reduction in health care costs with the clear possibility to dedicate more time and means to the remaining cases, so in average improving the quality and efficiency of healthcare.

The recording, interpretation and interconnecting possibilities of the system to be designed will provide an essential help for a health centre to objectively track the effect of the therapy, the patient compliance, changes in patient characteristics (like insulin resistance) etc. All this will be especially valuable, as it will allow the health professionals to use objective data and not only the partly subjective record by the patient.

5.4 Contributing to IDF-Europe strategy recommendations

Diabetes mellitus (DM) is a severe problem to Europe as well as globally. According to the European Health Report 2002 of the World Health Organization (WHO), in Europe more than 22.5 million people suffer from DM[22].

Europe's growing obesity epidemic, its aging population and our increasingly sedentary lifestyle have led to an explosion in the incidence of diabetes, particularly Type 2 diabetes, across the

[21] DCCT: The Diabetes Control and Complications Trial Research Group.The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329, 977-86.
[22] Austrian Health Institute, 2005. http://www.evotion.at/diabetes/downloads/Diabetesstudie_Englisch_19_1_06_pdf.pdf

European Union. With an average EU prevalence rate of 7.5%, a predicted growth rate of 16% by 2025, and up to 50% of diabetes cases currently undiagnosed[23], this crisis is a reality today.

The Commission's proposal for a Programme of Community Action in the field of Health and Consumer Protection (2007-2013) is intended to:

> "Improve the health of citizens throughout their lives, improve health as a human right and encourage investment in health"

and refers explicitly to the need for:

> "The promotion of policies which lead to a healthier way of life helping to reduce the incidence of major diseases"

Furthermore, the European Parliament's Environment, Public Health and Food Safety Committee recently agreed to amend the Programme, requesting the Commission to:

> "Submit, during the course of this Framework Programme, proposals for Council Recommendations on the prevention, diagnosis and control of major diseases"

Following consultation with key EU diabetes stakeholders and through the formation of an EU Policy Working Group, the following recommendation was developed, comprising experts in the field and national and EU policy makers. This working group has reached a broad consensus about the way in which the EU and its Member States can and should be addressing the diabetes epidemic[24]:

> "Facilitate and support European diabetes research in basic and clinical science and humanities of care. Ensure the wide dissemination of the results of this research across Europe. The EU and its Member States collectively offer great potential for the effectiveness and relevance of quantitative and qualitative research in diabetes, its prevalence and associated risk factors. The EU could make a major contribution to research relating especially to the behavioural and epidemiological impact of diabetes in Europe. With appropriate support and funding in this area, genuine added value can be achieved, not least due to the territorial and numerical (population) scale of EU action."

The DIAdvisor proposal will contribute to the recommendations made by IDF-Europe who was a partner in the DIAdvisor consortium.

5.5 Added value of a European level project

The project address an important problem at European level and it will bring direct benefits to diabetics across Europe. The core technology for continuously monitoring and correlating bio-chemical and vital sign data has enormous potential for improving the quality of healthcare and reducing costs.

The project needed to be carried out at European level, because very specific resources was needed that not all can be found in a on institution or even in any single country. Expertise from several countries needed to be combined and used for the construction of the system.

[23] IDF Atlas 2011
[24] IDF 2006 EU Policy recommendations http://www.fend.org/news_assets/diabetes_eu_policypaper.pdf

6. Project Public Website

The public project website can be found at: www.diadvisor.eu where links to a selection of publications can be found.

7. Consortium

Primary Partner contact	Role	website
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Prof. Rolf Johansson Lunds University, Lund, Sweden	Data based models	www.lu.se
Prof. Claudio Cobelli University of Padova, Padova, Italy	Physiological models	www.unipd.it
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Table 6: Consortium partners and roles